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Our Docket No. MIT 7501
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MESSAGE:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon

Serial No.: 08/823,999 Group Art Unit: 1644

Filed: March 25, 1997 Examiner: Philip Gambel

For: *MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION*

PTO/SB/21 (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/823,999
Filing Date	March 25, 1997
First Named Inventor	Campbell Rogers
Art Unit	1644
Examiner Name	Phillip Gambel
Total Number of Pages In This Submission: 44	Attorney Docket Number: MIT 7501

ENCLOSURES *(Check all that apply)*

- ☑ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
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  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
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Firm or Individual name	Rivka D. Monheit, Esq., Reg. No. 48,731 Pabst Patent Group LLP 400 Colony Square, Suite 1200, Atlanta, GA 30361
Signature	Rivka D. Monheit
Date	August 10, 2004

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☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 0

Complete if Known	
Application Number	08/823,999
Filing Date	March 25, 1997
First Named Inventor	Campbell Rogers
Examiner Name	Phillip Gambel
Art Unit	1644
Attorney Docket No.	MIT 7501

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1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

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Independent Claims	2	-3** =	0	X		=	0
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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FEE CALCULATION (continued)

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1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

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SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	Rivka D. Monheit	Registration No. (Attorney/Agent)	48,731	Telephone	(404) 879-2152
Signature	Rivka D. Monheit			Date	August 10, 2004

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THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon	
Serial No.:	08/823,999	Group Art Unit: 1644
Filed:	March 25, 1997	Examiner: Phillip Gambel
For:	*MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION*	

PREVIOUS APPEAL NO: 2003-0074

Mail Stop Appeal Brief-Patents
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SUBSTITUTE APPEAL BRIEF

Sir:

Responsive to the Notification of Non-Compliance with 37 C.F.R. § 1.192(c) mailed on July 27, 2004, this is a Substitute Appeal Brief to replace the Appeal Brief filed on July 21, 2004.

This is an appeal from the rejection of claims 1-12 in the Office Action mailed October 30, 2003 in the above-identified patent application. A Notice of Appeal was filed on January 30, 2004. An Appeal Brief was filed on July 21, 2004. The fee for filing of an Appeal Brief for a small entity was charged to Deposit Order Account No. 50-3129. A Petition for an Extension of Time for four months was filed on July 23, 2004. The fee for a four-month extension of time for

a small entity was charged to Deposit Order Account No. 50-3129. It is believed that no fee is required with this submission. However if a fee is required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real parties in interest of this application are Massachusetts Institute of Technology, Cambridge, MA and Brigham and Women's Hospital, Boston, MA.

(2) RELATED APPEALS AND INTERFERENCES

This application has previously been on appeal to the Board of Appeals as **APPEAL NO: 2003-0074.**

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-12 are pending and rejected. Claims 7 and 9 were withdrawn as directed to a non-elected invention. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment dated January 30, 2004.

(5) SUMMARY OF THE INVENTION

The compositions described herein are used to inhibit undesired response to vascular injury that includes hyperplasia of vascular smooth muscle cells which occurs in response to injury of blood vessels, for example, as a result of angioplasty, atherectomy, endovascular stenting coronary or peripheral arterial bypass used to open a stenotic or occluded vessel or transplantation of cells, tissue or organs (page 6, lines 13-18). Vascular smooth muscle cell

hyperplasia triggered by the injured vessel can result in stenosis or restenosis of the blood vessel (page 6, lines 19-20). These compositions and methods are based on the discovery that inhibition of integrin-mediated leukocyte adhesion and/or function, especially adhesion and function of monocytes and granulocytes, can significantly reduce restenosis. (page 6, lines 12-23).

Restenosis is an extremely complex phenomenon, involving numerous complex interactions (page 6, lines 24-250. Many "single target" therapies have been tried as a means to reduce the occurrence or severity of restenosis, unsuccessfully Page 6, lines 25-26). The extent of neointimal hyperplasia and cellular proliferation in animal models of vascular injury and repair is associated with the number of adherent and infiltrating monocytes. (page 6, line 24, to page 7, line 1) As described by appellants, inhibition of integrin-mediated leukocyte adherence or function can be used to decrease the amount of neointima formed following vascular injury (page 7, lines 7-12). These results are particularly striking in view of the complexity of the problem and the lack of success previously achieved using compounds blocking specific sites. (page 7, lines 7-12).

As defined by the claims, leukocyte adhesion or function can be inhibited or reduced by blocking cell surface integrins: Mac-1 (CD11b/CD18, αMβ2), LFA-1 (CD11a/CD18, αLβ2), p150,95 (CD11c/CD18, αXβ2) and CD11d/CD18, or their ligands (page 7, lines 14-21). Ligands for Mac-1 include, among others, ICAM-1, fibrin(ogen), C3bi, and factor X (page 7, lines 21-22). Ligands for LFA-1 include ICAM-1, ICAM-2, and ICAM-3 (page 7, lines 22-23).

Ligands for p150,95 include fibrin(ogen) and C3bi (page 7, line 23). Exemplary compounds for inhibiting or reducing leukocyte adhesion or function include antibodies and antibody fragments that are immunoreactive with these integrins or their ligands and which inhibit or reduce the binding of integrins or their ligands to vascular cells (page 7, linex 26-30; claims 8 and 10); molecules which inhibit or reduce the expression of the integrins or their ligands, including nucleic acid regulators such as antisense oligonucleotides, ribozymes and external guide sequences for RNAase P, molecules involved in triplex formation, aptamers, peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells such as peptides and peptidomimetics that block the leukocyte integrin Mac-1 (page 8, lines 1-6). The compounds can be administered systemically or administered directly to the site of vascular injury, most preferably prior to and after injury. (page 4, line 6-page 5, line 5).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) the rejection of claims 1-9, 11 and 12 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description;

(2) the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement;

(3) the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph, as indefinite;

(4) the rejection of claims 1-6, 8 and 10-12 under 35 U.S.C. §102(a)(b) (presumably one or the other) by Genetta, et al., Ann. Pharmacol. 30:251-257 (1996) in view of Schwarz, et al.,

Thrombosis Res. 107:121-128 (2002), Bendeck, et al., J. Vasc. Res. 38:590-599 (2001); Wu, et al., Thrombosis Res. 101:127-138 (2001); and the ERASER Investigators Circulation 100:799-806 (1999);

(5) the rejection of claims 1-6, 8 and 10 under 35 U.S.C. §102(b) as lacking novelty over Simon, et al., Circulation 92(8 Suppl), 1-110 abstract 0519 (1995) in view of in view of Schwarz, et al., Thrombosis Res. 107:121-128 (2002), Bendeck, et al., J. Vasc. Res. 38:590-599 (2001); Wu, et al., Thrombosis Res. 101:127-138 (2001); and the ERASER Investigators Circulation 100:799-806 (1999); and

(6) the rejection of claims 1-6, 8 and 10-12 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 5,976,532 in view of Schwarz, et al., Thrombosis Res. 107:121-128 (2002), Bendeck, et al., J. Vasc. Res. 38:590-599 (2001); Wu, et al., Thrombosis Res. 101:127-138 (2001); and the ERASER Investigators Circulation 100:799-806 (1999);

(7) the rejection of claims 1-6, 8 and 10-12 under 35 U.S.C. §102(e) as lacking novelty over U.S. Patent No. 6,210,671 to Co, et al.;

(8) the rejection of claims 1-6, 8 and 10-12 under 35 U.S.C. §102(b) as lacking novelty over U.S. Patent No. 4,935,234 to Todd, et al.; and

(9) the rejection of claims 1-6, 8 and 10-12 under 35 U.S.C. §103 as obvious over U.S. Patent No. 6,210,671 to Co, et al., and /or U.S. Patent No. 4,840,793 to Todd, et al., in view of Simon, et al., Circulation 92, 8 Suppl:1-110, abstract 0519 (1995); Mazzone, et al., Circulation 88:358-363 (1993); Ikeda, et al., Am. Heart J. 128:1091-1098 (1994); Inoue, et al., JACC 28:1127-1133 (1996); and Rogers, et al., Circulation 88:1215-1221 (1993).

The claims were also rejected on the grounds of obviousness type double patenting over U.S.S.N. 09/776,533. This issue has been reserved until allowable subject matter in either application has been indicated, particularly in view of the complicated and inconsistent restriction requirements and election of species made between the two identical applications and originally filed claims.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims are drawn to patentably distinct subject matter as discussed below.

Claim 1 is drawn to a method of treating a patient in need of treatment to inhibit or reduce restenosis of a blood vessel following injury to vascular tissue, by administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or educes leukocyte integerin-mediated adhesion or function.

Claims 2, 5, 6, 7, 9 and 10 define the integrins that can be used. Claims 7 and 9 have been withdrawn by the examiner as defining non-elected subject matter.

Claim 2 limits the integrins to those mediating adhesion to monocytes or granulocytes. Claim 5 (as well as claim 1, if amended as proposed by the accompanying amendment) limits the integrins to Mac-1, LFA-1, p150,95, and CD11d/CD18.

Claims 6 and 7 limit the integrin further to Mac-1 and specific Mac-1 ligands. Claim 10 is specific to antibodies to Mac-1.

Claim 9 limits the integrin to LFA-1.

Claims 3, 11 and 12, are specific to the patients to be treated, and treatment regimes, specifically defining the patients as those undergoing angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, and transplantation (claim 3); and the time of administration as prior to vascular intervention (claim 11) or prior to and after vascular intervention until healing has occurred (claim 12).

Claim 4 is specific to the type of pharmaceutically acceptable carrier in which the active compound is administered.

Claim 8 defines the active compound as an antibody or antibody fragment.

Since the claims are drawn to different subject matter, some of which does not raise issues under §112, such as claim 10, and others which contain limitations not disclosed at all by the prior art, such as claims 3 and 11, and other represent different combinations of elements in the art, the claims must be separately assessed for patentability, as discussed in more detail below.

(8) ARGUMENTS

(a) The Invention

The present invention is the discovery that a single compound can be used to prevent or inhibit restenosis. Restenosis is a very complicated disorder, known to have multiple causes and factors that can elicit or aggravate development of the disorder. Restenosis frequently develops following angioplasty, surgery and other vascular intervention. It is characterized as an accelerated arteriopathy characterized by rapid growth of cells into the lumen within a short period of time which is severe enough to jeopardize the blood flow to distal organs.

Restenosis is accompanied by the loss of normal endothelial function. The arterial endothelium serves as a transport barrier, a biochemical filter and as a regulator of many vascular phenomena. The most potent vasodilators, thromboresistant compounds and inhibitors of smooth muscle cell proliferation, are endothelial derived. Vascular smooth muscle cell accumulation within the intima ceases with restoration of the endothelium (Schwartz et al., *Am. J. Pathol.*, *81*: 15-42 (1975); Fishman et al., *Lab. Invest.*, *32*: 339-51 (1975)) and regression of intimal hyperplasia is maximized where endothelial restoration is maximized (Bjornsson et al., *Proc. Natl. Acad. Sci. USA*, *88*: 8651-8655 (1991)). Confluent, and not exponentially growing, endothelial cells produce a series of compounds that are the most potent vasodilators, inhibitors of spasm, and inhibitors of smooth muscle cell proliferation. Heparan sulfate proteoglycan produced by the endothelial cells has multitudinous effects on the smooth muscle cells including interfering with binding of heparin-binding growth factors (Nugent et al., *Circulation Research*, *73*: 1051-1060 (1993), which are known to stimulate vascular smooth muscle cell growth (Nugent et al., *Circulation Research*, *73*: 1051-1060 (1993); Castellot et al., *J. Cell Biol.*, *90*: 372-9 (1981)). It appears, therefore, that restoring the endothelial monolayer of a blood vessel restores the agents or compounds responsible for biochemical control of vascular cell proliferation.

Other efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds. Certain drugs, such as heparin, are especially effective inhibitors of vascular smooth muscle cell proliferation in tissue culture and animal models of arterial diseases precisely because they

mimic the activity of natural endothelial-derived compounds like heparan sulfate proteoglycan, Edelman, E.R. & Karnovskv, M.J. *Circ.* 89: 770-776 (1994). However, despite cell culture and small animal data supporting the regulatory role of heparin-like compounds, exogenous heparin preparations have shown no benefit in human trials. For example, when patients were randomized to heparin or dextrose infusion over the first 18 to 24 hours post angioplasty, 41.2% of the heparinized patients and only 36.7% of the dextrose infusion patients had evidence for restenosis (Ellis et al., *Am. Heart. J., 117*: 777-782 (1989)). Moreover, bleeding complications were twice as frequent in the heparinized group. In another trial, angioplasty patients injected subcutaneously with heparin at 10,000 IU/day had 2.5 fold more restenosis and significantly more ischemic complications than patients treated in the standard fashion (Lehmann et al., *J. Am. Coll. Cardiol., 17*: 181A (abstract) (1991)). Non-heparin endothelial compounds such as nitric oxide and the prostaglandins are potent regulators of a range of biologic effects involving smooth muscle cells. Inhibitors of these compounds have been shown to control intimal hyperplasia following experimental vascular injury (Cooke et al., *Curr. Opin. Cardiol., 7*: 799-804 (1992); Moncada et al., *N. Engl. J. Med., 329*: 2002-2012 (1993); McNamara, et al., *Biochem. Biophys. Res. Comm., 193*: 291-296 (1993)). This is indicative that the vascular endothelium is a powerful regulator of the blood vessel wall, not because of the production and secretion of one compound alone, but because of its presence as an intact unit.

Accordingly, one skilled in the art would not expect a single compound to be effective in limiting or preventing restenosis. Therefore the results obtained by appellants showing that a single class of compound, compounds blocking binding and activation of certain integrins, could

effectively limit restenosis were completely unexpected. Importantly, it is not administration of a single compound, but class of compounds, that achieves this effect. These compounds inhibit or reduce leukocyte adhesion or function by interference with integrin-mediated binding. Leukocyte adhesion and function can be inhibited or reduced by blocking cell surface integrins, such as the leukocyte integrin Mac-1 (CD11b/CD18, αMβ2), LFA-1 (CD11a/CD18, αLβ2), p150,95 (CD11c/CD18, αXβ2) and CD11d/CD18, or their ligands. Ligands for Mac-1 include, among others, ICAM-1, fibrin(ogen) C3bi, and factor X. Ligands for LFA-1 include ICAM-1, ICAM-2, and ICAM-3. Ligands for p150,95 include fibrin(ogen) and C36. Mac-1, also known as CD11b/CD18, CR3, and αm/β2, is a leukocyte adhesion molecule found on monocytes, neutrophils, and natural killer lymphocytes. Mac-1 binds heterogeneous ligands including, among others, fibrin(ogen), factor X, intercellular adhesion molecule-1 (ICAM-1), C3bi, and high-molecular-weight-kininogen. Suitable compounds include antibodies and antibody fragments that are immunoreactive with integrins or their ligands and which inhibit or reduce the binding of integrins or their ligands to vascular cells; molecules which inhibit or reduce the expression of integrins or their ligands, including nucleic acid regulators such as antisense oligonucleotides, ribozymes and external guide sequences for RNAase P, molecules involved in triplex formation, aptamers, and peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells.

Clarification of Terms

The Board of Appeals has made the following of record (see Paper No. 38).

A) Taber's Cyclopedic Medical Dictionary, 18th Ed., pp130, 166 and 1828 (1997) (892: of record) with respect to the following definitions.

Stenosis: The constriction or narrowing of a passage or orifice.

Aortic Stenosis: Narrowing of the aorta or its orifice due to lesion of the wall with scar formation.

Restenosis: The Recurrence of a stenotic condition as in a heart valve or vessel.

In response to the Board's request (page 3 of Paper No. 38), Appellants distinguish the terms "stenosis", restenosis" and "dependent restenosis" as follows.

Stenosis: Narrowing of a blood vessel for the first time. If a vein is transplanted in bypass surgery, it will be subject to stenosis because it will be the first time the transplanted vessel is narrowed.

Restenosis: Re-narrowing of a vessel after mechanical intervention for example with balloon, stent, atherectomy or laser.

Dependent restenosis has been removed from the claims.

Accelerated arteriopathies: Restenosis as well as stenosis (narrowing of vessel) of vein graft or stenosis following transplantation. Accelerated arteriopathies normally develop within months to a year and result in neointimal thickening. Conversely, atherosclerosis-mediated stenosis takes decades to develop.

The claims are directed to a method of inhibiting or reducing accelerated arteriopathies such as stenosis arising from , coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to a

vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, by administering a compound which specifically inhibits or reduces leukocyte integrin mediated adhesion or function in an effective amount to inhibit or reduce the accelerated artieriopathies of a blood vessel following injury to vascular tissue. The patient can be either human or animal model as the claims read on either. The reduction or inhibition of stenosis or restenosis can be a reduction or inhibition of narrowing of the blood vessel due to leukocyte integrin-mediated cell adhesion. An effective amount of an anti Mac-1 antibody is described on page 21, lines 4-16 as ranging between 0.25 mg/Kg to 1 mg/Kg and can be adjusted accordingly by one of skill in the art using routine methods.

One very important concept to recognize is the difference between accelerated arteriopathies such as restenosis and ischemic-reperfusion injury. The following table shows the differences between these two types of disorders.

Disorder	Ischemia-Reperfusion	Restenosis/Accelerated Arteriopathy
Cessation in blood flow?	Yes	No
Endothelium present?	Yes	No
Concern over target organ damage?	Yes	No

From the above table, it is very clear that Ischemia-Reperfusion and Restenosis are very different disorders with different mechanisms and characteristics. This point is very important for the ensuing discussion of prior art.

(b) Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled.

i. The Legal Standard

The standard for determining whether the specification meets the enablement requirement is whether the claimed invention enables any person skilled in the art to make and use the invention without undue experimentation. *In re Wands,* 858 F.2d 731, 8 USPQ 1400 (Fed. Cir. 1988). This case set out eight factors to be considered in determining whether enablement has been met. These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; (H) and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.* at 737.

The examiner rejected the claims of the application based on the allegation that is is an unpredictable art and the specification lacked working examples that would enable one to make the claimed invention. It is well established that one does not have to provide working examples in an application. If the invention can be reproduced using reasonable, but not undue experimentation, then the enablement requirement has been satisfied. *In re Angstadt,* 537 F.2d 498, 502, 190 USPQ 214 (CCPA 1976). Predictability of the art is dependent on the amount of guidance the specification provides to those skilled in the relevant area of art. (In this case, evidence has been submitted that animal models are predictive of results in humans). "The scope of enablement varies inversely with the degree of unpredictability of the factors involved." *In re*

Fisher, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970). However, as stated in *Angstadt,* a disclosure of every operable species is not required even in unpredictable arts. *Id.* at 502.

In *Amgen, Inc., v. Hoechst Marion Roussel Inc.,* 314 F.3d 1313 ,65 USPQ2d 1385 (Fed. Cir 2003), the Court held that the standard for enablement is two-fold: 1. "where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed"; and 2. "the specification need teach only one mode of making and using a claimed composition." *Id.* at 1329. *Amgen* further held that post-filing publications could be used to show enablement in an unpredictable area or art. *Citing Gould v. Quigg,* 822 F.2d 1074, 3 USPQ2d 1302 (Fed. Cir. 1987).

The Court in *Bryan Real v. Bunn-O-Matic Corp.,* 119 F.Supp.2d 807 (N.D. Illinois 2000), held that a "patent reference need not describe every last detail that would make the invention work in order to satisfy enablement requirement; rather, it may omit principles well known to those of ordinary skill so long as it describes enough information to allow one of ordinary skill in the art to make the invention." *Id.* at 811.

ii. The Claims Meet the Legal Standard for Enablement

Data has been submitted in the application and subsequently showing the efficacy of **two species of inhibitors, antibodies to Mac-1 and peptide inhibitors.** See the examples at pages 22-23 of the application as filed, using an antibody to Mac-1 to inhibit restenosis following vascular injury. An abstract published in Circulation, Supp. 1, vol. 100, no. 18 November 2, 1999, number 1742 (attached as Exhibit 1), has also been submitted demonstrating that an

equivalent effect can be obtained with a peptide inhibitor.

This is in addition to the lengthy discussion in the application as originally filed which defines the integrins and ligands (page 7, lines 13-25; page 8, line 7 to page 9, line 10; page 9, line 22-page 10, line 11); the classes of compounds, including antibodies (page 9, lines 11-22; page 10, line 10-page 11, line 19); peptides and peptidomimetics (page 11, line 20, to page 13, line 19); methods for screening for compounds and generation of synthetic compounds randomly and by computer aided design (page 13, line 20 to page 16, line 15), and nucleic acid molecules (page 16, line 16, to page 19, last line). Carrier materials are described on page 20. Methods for administration are detailed at page 20, line 22, to page 22, line 2.

iii. The Examiner has provided only allegations; not support for his rejections

No proper *prima facie* case for lack of enablement has been established. The Examiner has provided no evidence or convincing argument that the claimed method cannot be used for the *in vivo* purposes described in the specification. Rather, the Examiner has merely expressed the opinion that the claimed method is unpredictable. This clearly does not meet the standard to establish a *prima facie* case of lack of enablement.

No support for the lack of enablement is found in any of the office actions. In the January 2004 office action, the examiner asserts at page 11 that the protein might be inactivated or might not reach its target - ignoring the *in vivo* animal studies that have been submitted showing that no such problems exist. While the studies were done in animals, there is no reason to believe the same results would not be obtained in humans - and indeed, the claims are not limited to humans. The statements regarding difficulties in predicting the effects of antibodies ignores not only the animal

studies, but years of efficacy following administration of antibodies and peptides. Appellants are not claiming an anti-thrombotic (see last paragraph page 11).

The appellants who have developed and tested the claimed method have spent years as vascular surgeons, conducting research in the area of restenosis in addition to treating patients. It is ludicrous that they think the claimed method should work, while an examiner with no clinical training questions the results. The standard under 35 U.S.C. 112, however, is quite clear: the issue is whether or not one skilled in the art would be able to practice what is claimed, based on the disclosure, with a reasonable expectation of success - not whether or not an examiner (or, for that matter, the prosecuting attorney) could practice what is claimed.

In summary, the examiner discusses the need for *in vivo* data to demonstrate that a therapy will be effective, but ignores the fact that the examples in the application as originally filed are in fact *in vivo* (although a rabbit rather than a human). There is also discussion about the fact that it takes years of development to prove a clinical treatment. The truth of this is indisputable but not relevant: the fact is that the appellants have provided *in vivo* evidence in their application showing that an antibody to at least one of the claimed integrins was effective in an animal model and in combination with independent third parties have provided evidence that another completely different kind of molecule, a peptide, derived from the integrin ligand glycolipid-anchored urokinase receptor, was also effective. The examiner has not responded to the latter evidence.

1. Animal Models are Predictive of Efficacy

The rejection is initially based on the proposition that the animal models, specifically the rat and rabbit animal models used by appellants, do not correlate well with *in vivo* clinical trial

results. Enclosed in response were three papers and abstracts of two others: The abstract of Coats, et al., "Remodeling and restenosis: insights from animal studies" Semin. Interv. Cardiol. 2(3), 153-158 (1997), notes that animal studies in remodeling and its contribution to restenosis have been critical, and correlated with human studies. Farb., et al., "Pathology and Chronic Coronary Stenting in Humans," Circulation, 99:44-52 (1999), paper notes at page 51, col. 2, that "These data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting early after implantation (with a relatively longer duration of healing in humans)." The authors then note that there is a difference in the type of vascular injury in normal arteries of animals as compared to the response in human atherosclerotic arteries. (This may be one reason why there has been variable correlation with some reported models). Komatsu, et al., "Neointimal Tissue Response at Sites of Coronary Stenting in Humans" Circulation 98, 224-233 (1998), reports that animal models are generally predictive (page 230), with dogs being an exception (page 232). Kearney, et al., "Histopathology of In-Stent Restenosis in Patients with Peripheral Artery Disease", Circulation, 95:1998-2002 (1997) correlates results in humans obtained at autopsy with animal studies, beginning at the bottom of page 1999, col. 2. The abstract of Folts, et al., J. Am. Coll. Cardio. 33(2), 295-303 (1999), notes that an animal model, the cyclic flow model of coronary thrombosis, has been useful in predicting which agents are likely to be of benefit in clinical trials.

In summary, the literature supports the use of animal models as predictive of efficacy.

2. <u>Data demonstrates Efficacy of Inhibiting Integrin-mediated Inhibition</u>

Example 2, beginning on page 22 of the application, shows administration of an antibody to rabbits after arterial injury. The data demonstrated that there was a reduction in neointimal area after deep injury of nearly 40% relative to controls. This data alone indicates that the active agent can be effectively delivered. No adverse effects were noted.

Also provided to the examiner (and enclosed in Exhibit 3) was an article by the authors and others which was submitted to the J. Clin. Invest. entitled "Decreased neointimal formation in Mac-1 (-/-) mice reveals a role for inflammation in vascular repair after angioplasty. (published by Simon, et al., J. Clin. Invest. 105(3), 293-300 (February 2000)). This paper describes the role of inflammation in mechanical arterial injury, in particular Mac-1, which when absent results in significantly less intimal proliferation and thickening after injury.

3. <u>There are numerous protein therapies</u>

The relevance of the comments regarding potential degradation of compound, etc. at pages 3-4 of the office action is not clear. Many pharmaceutical proteins and numerous antibodies are administered to patients as therapeutics, absent side effects, and without loss of function, for example, as shown by the abstract by Topol, et al., "Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication" JAMA 278(6):479-484 (1997). (Exhibit 4)

Summary

In summary, the examiner has provided mere assumption, not specific support, for alleging that the application is non-enabling. Appellants have responded by pointing to the

specific support in the application as well as to supporting data. No rebuttal has been made by the examiner.

(c) Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-9, 11 and 12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

i. The Legal Standard

Enzo Biochem, Inc., v. Gen-Probe Incorporated,, 323 F.3d 956 (Fed. Cir. 2002) held that all functional descriptions of genetic material are not required in order to meet the written description requirement of §112.

The standard is met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics…i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 956.

The standard for determining compliance with the written description requirement is an objective standard. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). The court in *Vas-Cath* stated that the appellant's description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. *Id.* at 1563. An appellant is able to show possession of the claimed invention by "describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas

that fully set forth the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565 (Cal. 1997). The scope of the disclosure with which the claims of a specification need in order to meet the written description requirement is not entirely encompassing and thus can be broad in breadth. Generally, a specification may contain a written description of a broadly claimed invention without describing all species that claim encompasses. *Utter v. Hiraga et al.*, 845 F.2d 993 (Fed. Cir. 1988).

A broader interpretation of the written description requirement relating to biotechnology inventions resulted from *Enzo Biochem, Inc., v. Gen-Probe Incorporated*, 323 F.3d 956 (Fed. Cir. 2002), discussed below. This case resulted from the earlier vacated case of *Enzo Biochem, Inc. v. Gen-Probe*, 285 F.3d 1013 (Fed. Cir. 2002). *Enzo* involved a patent directed to nucleic acid probes that selectively hybridize to genetic material of bacteria that cause gonorrhea. *Id.* at 956. Enzo asserted that the written description of the claimed invention was met because there was a reference to deposits of the three sequences, which were within the scope of its claims.

The court in *Enzo* interpretsx this case more broadly and deviatex from the *Eli Lilly* standard for the written description requirement because the inventor deposited the derived biological materials. The deposited materials demonstrated possession of the invention in accordance with §112 requirements. The court ruled that it was "not correct ...that all functional descriptions of genetic material fail to meet the written description requirement." *Id.* at 959. Therefore, the disclosure of the sequence was not always necessary and other types of disclosures could be examined on a case by case basis. The *Enzo* court adopted provisions from the MPEP's guidelines that allow the written description requirement to be met by "showing that

an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

The Court in *Amgen, Inc., v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), also applied the broad interpretation of the written description requirement set out in *Enzo* regarding the type of disclosures that comply with this requirement. *Amgen* deals with an infringement action over plaintiffs' patents to erythropoietin (EPO), process for producing EPO, and cells for producing EPO. The defendants claimed that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention and relied on *Eli Lilly*. The court stated that *Enzo* clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement. Rather, "the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *See Enzo* at 1324. The *Amgen* case is distinguishable from both *Eli Lilly* and *Enzo* because the claim terms at issue "are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO." *Id.* This decision further adopts a broader interpretation of what's required for the written description to be satisfied.

b. The Claims Meet the Written Description Requirement

The specification supports the use of any "compound which specifically inhibits or

reduces leukocyte integrin-mediated adhesion or function". Detailed description is provided for compounds such as antibodies or antibody fragments (p9-11), peptide and peptidomimetic compounds (p11-p13) and nucleic acid regulators (p16-19) that inhibit or reduce leukocyte integrin-mediated adhesion or function. These compounds share the common feature that they all bind integrins or their ligands. These compounds were known and available as of the date of filing - it was not the discovery of these compounds, but of their selection and utility that appellants claim. One of skill in the art would know of other such compounds and how to make and use them as claimed, without undue experimentation.. The Examples in the specification describe in clear detail how one would use a "compound" (in this case Mac-1 antibody) to reduce or inhibit leukocyte integrin-mediated adhesion or function. Computer assisted drug design is described on page 15 wherein one can model drugs and their interactions with the integrins. This method describes a concrete means by which one can obtain a wide range of compounds that reduce or inhibit integrin-mediated adhesion or function. The Examples in the specification describe in detail and demonstrate reduction to practice of one such compound. As stated in the recent CAFC decision, adequate description of claims to species support the claims to the genus. In this case, several species have been described in detail in the specification. The legal standard is met.

The elected invention of anti-Mac-1 antibodies including soluble adhesion molecules and adhesion molecule-specific antibodies as well as the fibrinogen peptide discussed in the specification including the full breadth of the claimed "compounds", meets the written description provision of 35 U.S.C. 112, first paragraph.

(d) Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-12 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

i. *The Legal Standard*

The Court in *Exxon Research and Engineering Company v. United States,* 265 F.3d 1371 (Fed. Cir. 2001), defined the legal standard for definiteness as follows: "If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2." *Id. citing Miles Labs, Inc., v. Shandon, Inc.,* 997 F.2d 870 (Fed. Cir. 1994).

The court further stated that claims do not have to be plain on their face to be definite. Rather, "the claims need be amenable to construction, however difficult that task may be. If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.*

In *Genzyme corporation v. Transkaryotic Therapies, Inc.,* 346 F.3d 1094 (Fed. Cir. 2003), the court held that in order to discern a term's usage within a claim, one must apply the ordinary and accustomed meaning of the words amongst artisans of ordinary skill in the relevant art at the time of invention. *Id.* Further, the application may consistently and clearly use a term in a manner "either more or less expansive than its general usage in the relevant community, and thus expand or limit the scope of the term in the context of the patent claims." *Id.*

Furthermore, "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as

precise as the subject matter permits, the courts can demand no more." *Bausch & Lomb, Inc., v. Alcon Laboratories, Inc.*, 79 F.Supp 243 (W.D. NY 1999),. at 245 citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613 (Fed. Cir. 1985).

ii. The Claims are Definite

The claims are directed to a method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel by administering an effective amount of a compound that ***specifically*** inhibits or reduces leukocyte integrin-mediated adhesion or function thereby reducing stenosis or restenosis of a blood vessel after injury to vascular tissue. The claims are definite because they define the inhibition/reduction of stenosis/restenosis by ***specifically*** inhibiting or reducing leukocyte integrin-mediated adhesion or function. The method by which stenosis/restenosis is reduced is by inhibiting or reducing integrin-mediated leukocyte adhesion. This is defined in the specification on page 6, lines 13-23. The specific endpoint is to reduce leukocyte integrin-mediated adhesion or function. Claim 1 has been amended to emphasize this endpoint.

An effective amount of compound to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to a vascular tissue is also defined in the specification on pages 20 and 21 of the specification. The courts have previously held that the use of "an effective amount" complies with the requirements under 37 C.F.R. 112. This phrase is not indefinite nor is one required to provide an exact dosage and treatment profile.

As the Court of Appeals most recently stated, in Geneva Pharmaceuticals et al. v. GlaxoSmithKline et al., 349 F.3d 1373 at 1384 (Fed. Cir. 2003):

> "Our predecessor court has stated that "effective amount" is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation." *In re Halleck*, 57 CCPA 954, 422 F.2d 911, 914 (CCPA 1970)

The definitions of the terms "stenosis" and "restenosis" have been provided above. The features of restenosis are defined in the specification on pages 6 and 7. The key parameter that is encompassed in the disorders listed in claim 3 is the involvement of leukocyte integrin-mediated adhesion. The claims are drawn to the use of inhibitors of leukocyte integrin-mediated adhesion, a readily measurable function. The role of leukocyte adhesion is disussed in both human and animal models (page 3, lines 4-24 of the specification citing Inoue et al JACC 28(5):1127-1133.)

The common feature between the disorders listed in claim 3 is the role of integrin-mediated leukocyte adhesion. Administering a compound to specifically inhibit/reduce integrin binding will be effective to treat, at least to some degree, all of these disorders. The effective amount can be routinely titrated for each patient depending on the compound and route of administration regardless of the disorder, to achieve therapeutic efficacy. This is described in the specification on page 21, lines 4-16.

While Fattori (2003) states that the mechanisms of restenosis differ between balloon and in-stent catheter injuries, both models share the feature of leukocyte integrin-mediated adhesion although to different degrees. Balloon catheter injury causes greater cell adherence than in-stent injury. This is supported by the specification in Example 2 that shows that specific blocking of

integrin binding causes a 75% reduction in the balloon injured vessel but only a 40% reduction in the in-stent injured vessel. Although still significant, the decreased effect in in-stent injured vessels is a reflection of the reduced contribution of leukocyte adhesion in in-stent restenosis.

Claims 5 and 6 (and withdrawn claims 7 and 9) are quite clear as to what the target is. The claims define a method of administering a compound that reduces leukocyte integrin-mediated adhesion and function by specifically interfering with either the integrin or the integrin-ligand. The specification teaches very clearly that by blocking interaction of integrins and their ligands one can inhibit leukocyte adhesion and neointima formation thereby reducing restenosis (page 7, lines 7-12). Therefore a compound that interferes with either the integrin or the integrin receptor will impede the binding occurrence that results in cell adhesion and restenosis. For further clarification the term "their ligands" has been amended to "integrin ligands".

(e) Rejection Under 35 U.S.C. § 102

i. The Legal Standard for a rejection under 35 U.S.C. § 102

The Board cited in their previous decision on page 7 *Celeritas Tech. ltd v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361, 47 U.S.P.Q.2d 1516, 1522 (Fed. Cir. 1998). "It is well settled that a claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." It must be established that a prior art reference discloses ***each and every*** element of the claims for a rejection of claims to be properly founded under 35 U.S.C. §102. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987) (emphasis added); *Scripps Clinic & Research Found v Genentech Inc*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 927 F.2d 1576:

"Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." (Emphasis added)

"A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation."

"[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference." *Id at 1576*

ii. Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by Genetta et al., Ann Pharmacol 30, 251-257 (1996) in combination with Schwarz et al., Thromb Res 107, 121-128(2002), Bendeck et al,. J Vasc Res 38,590-599 (2001), Wu et al., Thromb Res 101, 127-138 (2001) and ERASER Investigators, Circulation 100, 799-806 (1999).

Genetta

Genetta discloses results of clinical trials using abciximab, a humanized chimeric Fab fragment of 7E3, a murine antibody to the integrin glycoprotein IIb/IIIa receptor (GPIIb/IIIa) located on ***platelets***, to reduce the incidence of abrupt closure and restenosis associated with PTCA. Abciximab was administered by bolus injection prior to and after angioplasty. Genetta does not disclose binding of Mac-1 by abciximab. Genetta does not disclose inhibiting

leukocyte adhesion; Genetta discloses inhibiting platelet aggregation. Platelets are not leukocytes. Adhesion (binding of the leukocytes to the cells lining the blood vessels) is not aggregation (clumping together of platelets).

Schwarz, Bendeck, Wu, and ERASER Investigations

Schwarz was cited to show that abciximab also binds to Mac-1. It is very clear based on the findings of Mickelson et al. (JACC 1999; 33(1):97-106, for example page 101, 1st column) that abciximab does not bind directly to Mac-1. The actions of abciximab on Mac-1 are indirect. No evidence has been provided that this indirect binding would "specifically" inhibit or reduce leukocyte integrin-mediated adhesion.

Bendeck and Wu were cited to show that abciximab can reduce smooth muscle cell migration following vascular injury. Once again, Mickelson states that amciximab does not directly bind to Mac-1. No evidence has been provided that inhibiting leukocyte adhesion reduces smooth muscle cell migration. Accordingly, there is no showing that abciximabl inhibits leukocyte adhesion nor that such inhibition is correlated with or related to a reduction in smooth muscle cell migration.

The ERASER study, originally cited by appellants, was cited by the examiner to establish that abciximab does not reduce in-stent restenosis. This seems to be further evidence for appellants' position that that abciximab does not bind directly to Mac-1, inhibit leukocyte adhesion or otherwise anticipate or make obvious the claimed subject matter. Appellants demonstrate in example 2 of the specification that their anti-Mac-1 antibody reduces both in-stent and balloon angioplasty injured restenosis.

The claimed method is not anticipated because Genetta does not disclose an antibody that ***specifically*** binds Mac-1 nor a compound that ***specifically*** inhibits or reduces leukocyte integrin-mediated adhesion or function. This claim element is not disclosed and is not an inherent feature of the antibody disclosed in Genetta.

The articles by Dietch et al. (Arterioscler Thromb Vasc Biol 1998 18:1730-1737), and Simon et al (J Clin Invest 2000 105:293-300) submitted by appellants demonstrate that abciximab has no effect on restenosis. These papers support the ERASER study previously made of record.

iii. Claims 1-6, 8 and 10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al., Circulation 92(8), 1-110 Abs 0519 (1995) in combination with Schwarz et al, Thromb Res 107,121-128 (2002), Bendeck et al, Wu et al and ERASER Investigators.

Simon et al (Circulation)

Simon, et al., (Circulation) reports on studies using an antibody fragment c7E3 immunoreactive with platelet glycoprotein IIb/IIa. Simon reports that the antibody was effective at reducing "**ischemic complications**" six months after coronary angioplasty and clinical restenosis. Simon also reports that the antibody is cross-reactive with Mac-1. The 7E3 Antibody does not inhibit restenosis. The 7E3 antibody is the foundation of the chimeric Fab fragment abciximab

The 7E3 antibody is known to inhibit integrin binding in cell culture, and be very effective in treating thrombotic conditions. However, treatment of thrombotic complications

(i.e., ischemia and ischemia-reperfusion injury) is not the same as, nor predictive of, treatment of patients to prevent or reduce restenosis, as compared above. The abstract does not report treatment of patients, the dosages, the times of administration nor indeed is that the focus of the abstract. The abstract reports ***in vitro*** studies that identify the activity of the antibody as cross-reactive with Mac-1 as well as platelet glycoprotein IIb/IIa. The patent describes treatment of a different class of patients, at different administration times and dosages. Therefore Simon et al. (Circulation) does not anticipate claims 1-12.

Thrombolysis causes injury due to a disruption in blood flow, followed by reperfusion, where the endothelium is intact. As described above, restenosis is injury arising when there is disruption in the endothelium while the blood flow remains continuous. Restenosis involves recruitment of platelets and leukocytes. As shown by the abstract, Mickelson, et al., "Chimeric 7E3 Fab (ReoPro) decreases detectable CD11b on neutrophils from patients undergoing coronary angioplasty", J. Am. Coll. Cardiol. 33(1):97-106 (1999), previously submitted by Appellants, this antibody decreases detectable CD11b on neutrophils but does not bind to neutrophils nor inhibit adhesion, two of the major factors involved in restenosis. See also Deitch, et al., "Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and intra-arterial stenting in atherosclerotic nonhuman primates", Arterioscler. Thromb. Vasc. Biol. 18(11):1730-7 (1998 Nov). As further shown by the paper, The Eraser Investigators, "Acute Platelet Inhibition with Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation 100:799-806 (1999), this antibody did not inhibit restenosis.

This evidence demonstrates that this antibody ("Reopro") does not affect restenosis and

that this is not an inherent property of the antibody. Therefore Simon, et al., does not disclose the claimed method.

iii. Claims 1-6, 8, and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,976,532 to Coller et al in combination with Schwarz et al. Thromb Res 107, 121-128 (2002), Bendeck et al, Wu et al and ERASER Investigations.

Coller et al

Coller et al., describes the 7E3 antibody which is discussed by Simon, et al., (Circulation). The patent reports that the antibody specifically binds glycoprotein IIb/IIIa and can be used as an antithrombotic agent. There is no disclosure of the use of the antibody to inhibit or prevent restenosis, nor of inhibiting leukocyte adhesion by interference with integrin binding..

As described above, the 7E3 antibody disclosed by Coller ("Reopro") does not affect restenosis and this is not an inherent property of the antibody. Furthermore, absent a disclosure of inhibiting stenosis or restenosis, Coller can not disclose "a method of inhibiting or reducing stenosis or restenosis". The legal standard for novelty is met.

iv. Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,210,671 to Co et al.

Co et al.

Co describes the use of humanized immunoglobulins to L-selection (which inhibit platelet aggregation) in the treatment of ischemic-reperfusion injury. Co describes administration of antibodies in combination with thrombolytic or angioplastic treatment for

restenosis, not in place of it. The Examiner admits that Co et al. does not disclose the limitations of stenosis and restenosis (page 27, Office action 10/30/2003). As Co does not disclose the same method defined in the present claims, the claimed method is not anticipated.

v. Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,935,234 to Todd et al.

Todd et al.

Todd et al discloses methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocytic-mediated inflammatory conditions, including inflammation from myocardial infarction or ischmia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD116/CD18 antibodies (col. 5, lines 49-53). The Examiner has admitted on page 28 of the Office Action that Todd does not disclose the limitation of treating restenosis. Todd discloses the use of the anti-CD116/CD18 antibodies to decrease the inflammatory response and infarct size, not decrease cell adhesion or stenosis/restenosis. Todd states that occlusion causes myocardial infarction in an experimental canine model for myocardial infarct.

Since Todd does not disclose each and every claim limitation, Todd does not anticipate the claimed method.

(f) Rejection Under 35 U.S.C. § 103

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 103(a) as obvious over Co *et al.* and/or Todd *et al.* in combination with Simon *et al.*, Mazzone *et al*, Circulation 88, 358-363 (1993), Ikeda *et al.*, Am Heart J 128, 1091-1098 (1994), Inoue *et al.*, JACC 28,1127-1133 (1996)

and Rogers *et al.*, Circulation 88, 1215-1221 (1993).

i. The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest ***all elements of the claimed invention*** and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992)(Emphasis added). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application

of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. In this case, there is simply no such teaching.

ii. *The Prior Art*

Co

Co is described above. Co does not teach using a single agent to inhibit or reduce stenosis or restenosis after injury.

Todd, III, et al.

Todd is described above. Todd does not describe the use of antibodies to inhibit or reduce stenosis or restenosis after injury.

Simon et al.

Simon is discussed above. Simon does not describe an antibody that inhibits restenosis nor specifically binds to integrin to block leukocyte mediated adhesion.

Mazonne

Mazonne does not disclose treating restenosis and does not disclose antibodies specific to Mac-1.

Ikeda

Ikeda discloses an increase in surface expression of CD11b after PTCA. Ikeda is an early study that shows that leukocytes are activated by angioplasty. Ikeda shows that Mac-1 is a non-specific marker of leukocyte activation. No data has been shown that Mac-1 is involved in restenosis.

Inoue

Inoue does not teach an antibody specific to Mac-1.

Rogers

Rogers does not disclose an antibody specific to Mac-1.

iii. There is no motivation to combine the references

It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the "level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-site Corp v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re*

Fritch, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. In this case, there is no teaching in the prior art that would suggest combining the references, with a reasonable expectation of success.

Efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds. Certain drugs, such as heparin, are especially effective inhibitors of vascular smooth muscle cell proliferation in tissue culture and animal models of arterial diseases precisely because they mimic the activity of natural endothelial-derived compounds like heparan sulfate proteoglycan, Edelman, E.R. & Karnovskv, M.J. *Circ.* 89: 770-776 (1994). However, despite cell culture and small animal data supporting the regulatory role of heparin-like compounds, exogenous heparin preparations have shown no benefit in human trials. Non-heparin endothelial compounds such as nitric oxide and the prostaglandins are potent regulators of a range of biologic effects involving smooth muscle cells. Inhibitors of these compounds have been shown to control intimal hyperplasia following experimental vascular injury (Cooke et al., *Curr. Opin. Cardiol.*, *7*: 799-804 (1992); Moncada et al., *N. Engl. J. Med.*, *329*: 2002-2012 (1993); McNamara, et al., *Biochem. Biophys. Res. Comm.*, *193*: 291-296 (1993)). This is indicative that the vascular endothelium is a powerful regulator of the blood vessel wall, not because of the production and secretion of one compound alone, but because of its presence as an intact unit.

One skilled in the art would not expect only a single compound to be effective in limiting

or preventing restenosis. This is demonstrated by Co et al. where antibodies are administered in combination with thrombolytic agents or angioplasty. The results obtained by appellants showing that a single class of compound, compounds blocking binding and activation of certain integrins, could effectively limit restenosis were completely unexpected. Importantly, it is not administration of a single compound, but class of compounds, that achieves this effect. These compounds inhibit or reduce leukocyte adhesion or function by interference with integrin-mediated binding.

(9) SUMMARY

Claims 1-12 are enabled by the specification, are definite, and comply with the written description requirement of 35 U.S.C. 112. No evidence has been provided by the examiner to support the rejection, and appellants have provided a detailed description in the application and in supporting data in the application and as subsequently published in support of the breadth of their claims.

Claims 1-12 define a method of preventing or inhibiting restenosis that is neither disclosed by, nor obvious from, the prior art cited by the examiner. Coller and Simon, et al. (Circulation) do not inherently disclose the claimed method. The other art cited by the examiner fails to make up for the deficiencies of Coller, et al. and Simon, et al.

(10) CONCLUSION

Claims 1-12 should be determined to be patentable under 35 U.S.C. §§ 112, 102 and 103.

Respectfully submitted,

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